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The role of tumor microenvironment IL-1β in Colorectal Cancer

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Abstract

Colorectal cancer (CRC) is the third leading cause of cancer, with high mortality due to metastasis development, mostly in the liver. Treatment with chemotherapy frequently results in chemoresistance, showing the importance of developing novel therapeutic approaches.
Inflammation has been shown to be a major factor in the development of many cancers, including CRC. Interleukin-1β (IL-1β) and Interleukin-1α (IL-1α), in their secreted form are abundant in the tumor microenvironment, where they can promote tumor growth, or (in some instances) can be involved in anti-tumor activities. In this study, we assessed the role of IL-1 in tumor progression.
After orthotopical injection of MC38 cells, wild-type (WT) mice developed local CRC with progression to liver metastasis. In contrast, in IL-1β knockout (KO) mice, there was retardation of tumor growth with no metastatic lesions in the liver. It is noteworthy that patterns of tumor growth in mice deficient in IL-1α are similar to those of WT mice. We assessed how IL-1β signaling affects various inflammation factors in the tumor microenvironment (TME) and its effects on colon microbiota. We found a significant decrease in inflammation in TME deficient in IL-1β. In addition, IL-1β is intensively involved in chemokine expression and thus in recruitment of inflammatory cells into TME. Reduced inflammation in IL-1β KO mice leads to a shift in colon microbiota, and we observed the prevalence of phyla that were shown to have some anti-carcinogenic properties.
Next, we assessed whether effects of IL-1β on CRC are specifically dependent on the origin of microenvironment. Thus, mice were injected intra-splenic with MC38 cells and experimental liver metastases were assessed. In this model, no differences or even a higher metastasis rate was observed in IL-1β KO mice in comparison to WT mice. These findings suggest that the effects of IL-1β in CRC are dependent on the site of tumor inoculation and specific TME immune response.
In conclusion, we suggest that IL-1β signaling is strongly connected to the local microenvironment and especially to the microbiome. IL-1β supports inflammation by inducing a cascade of other pro-inflammatory molecules, which recruit pro-inflammatory immunosuppressive cells into TME. This inflammatory environment affects the colon microbiota, which becomes pro-tumorigenic. Inhibition of IL-1β can prevent these changes, improve disease outcome and alleviate side effects of chemotherapy.